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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,868	11/28/2001	Cornelia M. Gorman	11669.103USW3	6177

7590 12/14/2004

Attention: Katherine M. Kowalchyk
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EXAMINER	
GUCKER, STEPHEN	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,868	GORMAN ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-43* is/are pending in the application.

4a) Of the above claim(s) *2-31 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group V, claims 32-37, filed 9/21/04 is acknowledged. The traversal is on the ground(s) that Group VI, claims 38-43, is classified in the same class and subclass as the subject matter of elected claims 32-37 and there would be no search burden on the Examiner to search these claims as well. This is not found persuasive because there exists extensive non-patent literature in genetic engineering that must be searched in addition to the U.S. patent prior art. In addition, foreign patent prior art that does not use the U.S. classification system must also be searched. Finally, the Examiner's search for Group V yielded prior art that is applicable to Group V, but would not be applicable for Group VI, so the searches for the two groups are not co-extensive and overlapping and therefore would constitute a search burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for these reason(s): pages 85-86 of the specification contain nucleotide sequences that require SEQ ID NOs.

3. Applicant should review the instant Application in its entirety for compliance with the sequence rules, paying particular attention that all sequences recited throughout the disclosure in its entirety have SEQ ID NOs and that the SEQ ID NOs recited are found in both the CRF and paper copy of the

Sequence Listing. Applicant must comply with the sequence rules and the remainder of the entire Office action simultaneously. Otherwise, Applicant will receive a Notice of Non-Responsive Reply.

4. Applicant is given the shortened statutory period of THREE MONTHS from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 32-37 recite "prorelaxin" in order to describe the nucleic acid encoding the polypeptide. However, the specification only describes the nucleotide and amino acid sequence for human prorelaxin, and it is the Examiner's belief that the state of the prior art at the effective filing date of the instant

Application (December 6, 1991) was that only rat, porcine, and human species of prorelaxin had been successfully cloned. Therefore, the disclosure lacks an adequate written description for host cells or methods that would produce other species forms of prorelaxin because the specification cannot describe in sufficient detail what the encoding sequences would be for these other forms of prorelaxin. Applicant is cautioned against simply amending the claims to recite "human prorelaxin" because a scope rejection would be made due to the overly broad definition of "human prorelaxin" given on page 32, line 30 to page 33, line 7 of the specification.

6. Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated animal host cells and methods producing chemically or structurally defined prorelaxin, does not reasonably provide enablement for transgenic primates, including humans, or prorelaxin that is not adequately characterized by structural or chemical means, for example, by a SEQ ID NO. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regards to the recitation of an animal host cell, the claims encompass embryonic stem cells and the cells of a transgenic animal *per se* (because all animals are made up of cells) such as a genetically altered primate, including humans (see page 33, line 31 to page 34, line 31 of the instant specification), which would include transgenic humans. The disclosure does not provide an adequate written description, guidance, or any working examples by which the genetic engineering or the gene

therapy required to accomplish this could be reasonably placed into the hands of the public because of the well known difficulties and unpredictability of successfully performing this kind of gene therapy on primates, including humans. The technical hurdles to be overcome include the manufacture of a suitable genetic vector, adequate transfection of host tissue, adequate expression of the genetic vector, etc. The grounds of this portion of the rejection could be simply obviated by amending the claims to recite "an isolated animal host cell." In addition, if Applicant intends for the instant claims to encompass any transgenic animals, the claims would be subject to a further restriction requirement as the examination of transgenic animals is beyond the scope of this examination and is a patentably distinct and separate invention from the instant invention.

Claims 32-37 recite "prorelaxin" in an attempt to characterize the nucleic acid encoding the polypeptide. However, the specification only provides adequate support for the nucleotide and amino acid sequence for human prorelaxin, and it is the Examiner's belief that the state of the prior art at the effective filing date of the instant Application (December 6, 1991) was that only rat, shark, porcine and human species of prorelaxin had been successfully sequenced. Therefore, the instant claims are not commensurate with the disclosure, as the claims are overly broad in that they encompass host cells and methods of making all forms of prorelaxin from every animal species, including prorelaxin with unlimited amino acid additions, deletions, and substitutions (see page 32, line 30 to page 33, line 7 of the specification). Because of the inherent unpredictability of trying to determine the biological functions of an amino

acid sequence with unlimited additions, deletions, and substitutions, the claims are not enabled to their full reasonable scope using the definitions provided by Applicant because undue experimentation would be required in order to determine which domains of the prorelaxin structure could be altered and which domains need to stay invariant in order to preserve biological functionality. Applicant is cautioned against simply amending the claims to recite "human prorelaxin" because a scope rejection would still be made due to the overly broad definition of "human prorelaxin" provided by the specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-37 are indefinite because it is not clear if by "animal host cell" the Applicant is intending to claim isolated host cells *in vitro* or is trying to claim whole transgenic animals or both. Amending the claim to recite "isolated animal host cell" would obviate the grounds of this rejection.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudson et al. (US 4,871,670, "Hudson") in view of Mulvihill et al (PTO-1449, filed 6/25/02, EP 319,944, "Mulvihill"). Hudson teaches the nucleic acid sequences for human relaxin and prorelaxin (abstract, Figures 2-3, and columns 15-18) and the transfection of bacteria in order to make the A, B, and C polypeptide chains of relaxin which can then be covalently linked by chemical means to make mature relaxin (column 6, lines 12-59 and column 13, line 14 to column 14, line 40). Hudson does not teach cells or methods using the cleaving endoprotease KEX2 or human embryonic kidney 293 cells. Mulvihill teaches the encoding sequence for KEX2 and methods using 293 cells transfected with KEX2 as a general method to prepare multi-chain polypeptides such as protein C (abstract, page 4, lines 30-48, page 5, lines 35-46, page 7, lines 14-15, page 8, lines 26-40, and pages 14-19) without resorting to the chemical linking steps of Hudson. Mulvihill does not teach host cells or methods of making prorelaxin or relaxin. It would have been obvious at the time the invention was made for one of ordinary skill in the art to make isolated animal host cells that produced relaxin by using the sequence information from Hudson in the 293 cells transfected with KEX2 as disclosed by Mulvihill for the many advantages taught by Mulvihill for the use of co-

expression in mammalian cells as compared to single expression in mammalian cells (abstract, page 2, lines 4-41, and page 4, lines 32-37). Additionally, the fact that the teachings of Mulvihill exclude the use of the cumbersome and low yield chemical linking through disulfide bonding steps of Hudson render the combination of the references *prima facie* obvious for ordinary artisans motivated to streamline the production steps and costs of the production of recombinant proteins and the genetically engineered host cells that produce said proteins.

9. Claims 32-33 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudson in view of Mulvihill and further in view of Thomas et al.(PTO-1449, filed 6/25/02, *PNAS* 88:5297-5301 (1991), "Thomas"). The teachings of Hudson and Mulvihill are as set forth in **¶8** above. Hudson and Mulvihill do not teach host cells or methods using prohormone convertase 1 (PC1), also known as PC3. Thomas does teach heterologous expression of transfected polypeptides with transfected PC1/PC3 and PC2. It would have been obvious at the time the invention was made for one of ordinary skill in the art to make isolated animal host cells that produced relaxin by using the sequence information from Hudson in the 293 cells as disclosed by Mulvihill with the PC1/PC3 and PC2 taught by Thomas because Thomas discloses that a combination of the different processing enzymes produces more efficient conversion of a prohormone into a mature hormone (abstract). Also, the many advantages taught by Mulvihill for the use of co-expression in mammalian cells as compared to single expression in mammalian cells (abstract, page 2, lines 4-41, and page 4, lines 32-37) would apply here too. Finally, the fact that the teachings of Mulvihill exclude the use of the

cumbersome and low yield chemical linking through disulfide bonding steps of Hudson render the combination of the references *prima facie* obvious for ordinary artisans motivated to streamline the production steps and costs of the production of recombinant proteins and the genetically engineered host cells that produce said proteins.

10. No claim is allowed.

11. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961. The fax phone number for this Group is currently (571) 273-8300.

SG

Stephen Gucker

December 13, 2004

Brenda Brumback

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